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This is the Accepted version of the following publication

Pedisic, Zeljko, Shrestha, Nipun, Kovalchik, Stephanie, Stamatakis, E, Liangruenrom, Nucharapon, Grgic, Jozo, Titze, S, Biddle, Stuart, Bauman, AE and Oja, P (2019) Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better? A systematic review and meta-analysis. British Journal of Sports Medicine. ISSN 0306-3674

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This article has been accepted for publication in British Journal of Sports Medicine in 2019, following peer review, and the Version of Record can be accessed online at <http://dx.doi.org/10.1136/bjsports-2018-100493>.

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Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better? A systematic review and meta-analysis

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ABSTRACT

Objective To investigate the association of running participation and the dose of running with the risk of all-cause, cardiovascular, and cancer mortality.

Design Systematic review and meta-analysis.

Data sources Journal articles, conference papers, and doctoral theses indexed in Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, PsycINFO, PubMed/MEDLINE, Scopus, SPORTDiscus, and Web of Science.

Eligibility criteria for selecting studies Prospective cohort studies on the association between running or jogging participation and the risk of all-cause, cardiovascular, and/or cancer mortality in a non-clinical population of adults were considered eligible for inclusion.

Results Fourteen studies from six prospective cohorts with a pooled sample of 232,149 participants were included. In total, 25,951 deaths were recorded during 5.5–35 year follow-ups. Our meta-analysis showed that running participation is associated with 27%, 30%, and 23% lower risk of all-cause (pooled adjusted hazard ratio [HR] = 0.73; 95% confidence interval [CI]: 0.68, 0.79), cardiovascular (HR = 0.70; 95% CI: 0.49, 0.98), and cancer (HR = 0.77; 95% CI: 0.68, 0.87) mortality, respectively, compared to no running. A meta-regression analysis revealed no significant dose-response trends for weekly frequency, weekly duration, pace, and the total volume of running.

Conclusion Increased rates of participation in running, regardless of its dose, would likely lead to substantial improvements in population health and longevity. Any amount of running, even just

once per week, is better than no running, whilst higher doses of running may not necessarily be associated with greater mortality benefits.

What is already known
<ul style="list-style-type: none">- It is unclear how running participation and the dose of running are associated with the risk of all-cause, cardiovascular, and cancer mortality
What are the new findings
<ul style="list-style-type: none">- Running participation is associated with 27%, 30%, and 23% reduced risk of all-cause, cardiovascular, and cancer mortality, respectively- Significant reductions in mortality risk can be expected for any dose of running, even just once per week or 50 minutes a week- We found no evidence that mortality benefits increase with higher amounts of running

INTRODUCTION

Global and national public health authorities recommend adults to engage in 150 minutes of moderate- to vigorous-intensity physical activity (MVPA) a week.[1-5] The epidemiological literature strongly supports the beneficial associations of total amount of MVPA with health outcomes.[6-10] Several systematic reviews and meta-analyses have summarized the evidence on the association between MVPA and the risk of disease-specific and all-cause mortality.[11-16] For example, a meta-analysis found that insufficient MVPA (defined as not meeting the current WHO guidelines for MVPA[1]) is associated with a 28% higher risk of all-cause mortality compared to sufficient MVPA.[15] Considering the high levels of physical inactivity globally, Lee and colleagues estimated that more than 5 million premature deaths a year would be prevented if insufficiently physically active people were to become sufficiently active.[15] Beyond the total amount of MVPA, there has been considerable interest in how different types of physical activity (e.g. walking, cycling, running, swimming) affect health and risk of premature mortality.[17-24] In other words, for any given amount of MVPA, does it matter for health what types of physical activity people do?

Running is among the most popular types of physical activity. For example, it has been estimated that each month around 3.7 million (8.5%) English adults participate in running as a sport or recreational activity.[25] Other countries, such as Australia[26] and the US,[27] have comparably high participation rates. The 2017 Physical Activity Council's survey ranked running in the top ten preferred activities that 25-44-year-old US adults who did not participate in sports or exercise wished to engage in.[28] Given its popularity, running as a sport and recreational activity has great potential for improving population health. The Royal College of General Practitioners (RCGP) has

acknowledged this potential by partnering with the *parkrun UK* initiative, to promote the uptake of running and walking among general practitioners and their patients.[29]

In a systematic review of observational and intervention studies published in 2015, Oja et al.[17] concluded that the evidence on health benefits is scarce for participation in all sports except for running and football. The authors concluded that there is: [i] moderate evidence for the associations between running and improved aerobic fitness, cardiovascular function, and running performance; [ii] limited evidence for the associations of running with improvements in metabolic fitness, adiposity status, and postural balance; and [iii] inconclusive evidence for the associations of running with cardiac adaptation, muscular strength, and disease-specific and all-cause mortality.[17] Oja et al.[17] identified only one study on running participation and the risk of mortality. A subsequent, comprehensive narrative review summarised the evidence on the association of running and a range of health outcomes, including major cardiometabolic outcomes, bone and respiratory health, disability, as well as disease-specific and all-cause mortality.[22] The strength of the association between running participation and the risk of all-cause and disease-specific mortality varied across different studies.[22] To date, no meta-analysis has synthesised evidence on the association between running participation and the risk of mortality.

From public health and exercise prescription perspectives, identifying the optimal doses of running for improved health outcomes is crucial. The “dose” of running is usually defined by its frequency (e.g. two times a week), overall duration in a given period (e.g. 40 minutes/week), pace (e.g. 10 km/h), and the total volume (e.g. expressed as the product of the overall weekly duration of running and the metabolic equivalent [MET] of running at a given pace; 800 MET-minutes/week).[30, 31]

It is plausible that higher running doses would lead to better health outcomes, such as improved physical and metabolic fitness, that are on the causal pathway between physical activity and lower mortality risk.[32] Contrary to this assumption, in 2015, Schnohr et al.[31] suggested there may be a U-shaped relationship between the dose of running and the risk of all-cause mortality. Compared to “sedentary” nonrunners, those who ran less than 2.5 hours a week, those who ran less than four times a week, and those who ran in a slow or average pace had significantly lower risks of all-cause mortality.[31] No statistically significant adjusted hazard ratios (HRs) were found for those who ran 2.5 or more hours a week, those who ran four or more times a week, and those who ran in a fast pace.[31] The U-shaped relationship may be explained by possible pathological changes in cardiovascular tissues induced by extreme doses of endurance sports over a long term; for example, by the development of patchy myocardial fibrosis that can trigger heart arrhythmias.[33] However, a relatively small number of participants in the Schnohr et al.[31] study were classified as “strenuous” runners and only a few death cases were registered in this group, limiting the statistical power of the analysis. The finding has sparked a lot of discussion among researchers.[22, 30, 34-40] To date, the available evidence on the dose-response relationship between running and the risk of mortality has not been synthesised in a meta-analysis.

The aim of this systematic review and meta-analysis was, therefore, to synthesise available evidence on the association of running participation and the dose of running with the risk of all-cause, cardiovascular, and cancer mortality.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[41] The review protocol has been registered in the International Prospective Register of Systematic Reviews – PROSPERO (registration id: CRD42016049965).

Literature search

We systematically searched PubMed/MEDLINE, Scopus, EBSCOHost (including Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, PsycINFO, and SPORTDiscus), and Web of Science for journal articles and conference papers published from the database inception to February 2019. Additionally, we searched for doctoral and master theses through Networked Digital Library of Theses and Dissertations (NDLTD) and Open Access Theses and Dissertations (OATD) databases. The searches were performed by combining the keywords “running”, “jogging”, “runner*”, and “jogger*” with the keywords “mortalit*”, “death*”, and “fatal*”. The search syntax can be found in online supplementary file 1. The reference lists of all included studies were checked to identify any titles that were not considered for inclusion in the primary literature search. The discrepancies of the literature search from the registered protocol are specified in online supplementary file 2.

Study selection

Two authors (ZP, NS) independently assessed the identified publications for relevance. When needed, the authors resolved disagreement by consulting and discussing with a third author (JG). Studies meeting the following criteria were included in the present review: 1) a prospective cohort

study; 2) adult sample (≥ 18 years of age); 3) non-clinical study population (i.e. a population not defined by the presence of a disease or a health condition); and 4) reported the association between participation in running or jogging and the risk of all-cause, cardiovascular, and/or cancer, mortality.

Data extraction

Using a predefined form, two authors (ZP and NS) independently extracted the following data from the included studies: 1) study date and location; 2) type of sample, sample size, and gender distribution; 3) age of study participants (range and mean \pm standard deviation); 4) duration of follow-up; 5) number of person-years; 6) number of runners and nonrunners in the sample; 7) number of mortality events in the total sample, among non-runners, and among runners; 8) the method of running assessment; 9) the mode of outcome assessment; 10) adjustments for potential confounding variables; 11) type of statistical analyses; and 12) key results on the association between running participation and the dose of running with the risk of all-cause, cardiovascular, and cancer mortality (online supplementary tables 1 and 2). Discrepancies in the extracted data were resolved by consulting and discussing with a third author (JG). Where needed, we also contacted authors of included studies to provide unpublished data.

Assessment of study and evidence quality

Two authors (NL and SJHB) independently assessed the quality of included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.[42] Details about the scale items and the scoring system can be found elsewhere.[42] The appraised studies were classified based on their overall score on the NOS scale as being of “poor quality” (0-3 points), “fair quality”

(4-6 points), or “good quality” (7-9) points. Discrepancies in the results of the two independent quality assessments were resolved by a third author (JG).

Assessment of adjustments for confounding

The appropriateness of adjustments for confounding in each study was assessed against directed acyclic graphs (DAG).[43] A possible representation of the directions of relationships is presented in figure 1. According to this DAG, for estimating the effect of running (through subsequent health status) on mortality risk, it would be necessary to adjust for sociodemographic factors, unhealthy lifestyle, adiposity, health status, and physical activity other than running.

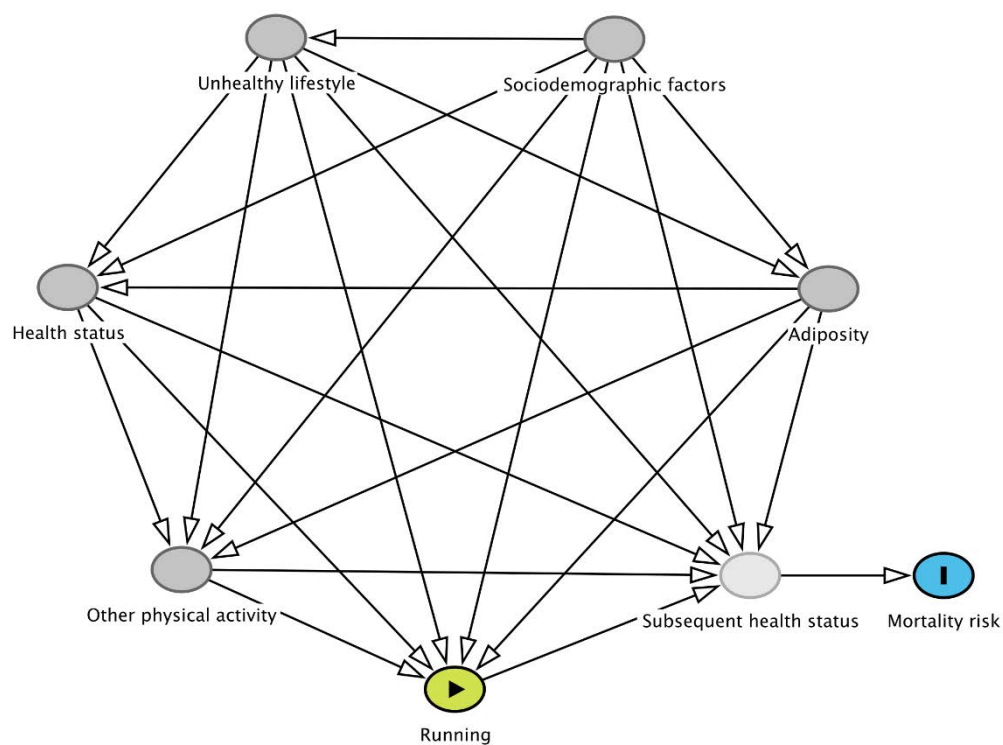


Figure 1 Directed acyclic graph (DAG) for the relationship between running participation and mortality risk. Green circle = exposure; blue circle = outcome; light grey circle = unobserved variable; dark grey circle = other variable; arrow = the direction of the causal relationship

Data analysis

If multiple analyses were conducted on the same cohort and published separately, our meta-analyses included estimates from the publication with the longest follow-up. We pooled individual HRs from the models that satisfied (or were the closest to satisfying) the adjustment requirements specified according to the DAG in figure 1; which is likely to provide conservative estimates. We did this using a random-effects meta-analysis, separately for all-cause, cardiovascular, and cancer mortality. We carried out the following additional analyses for all-cause mortality:

- (a) a subgroup analysis by gender;
- (b) a sensitivity analysis where we only included the studies classified as “good quality”;
- (c) a sensitivity analysis where we included the most recent study from the Copenhagen City Heart Study cohort[44] instead of the one with the longest follow-up and the largest sample size.[45];
- (d) a sensitivity analysis where we included HRs from an alternative model in the Lee et al. [46] study (see description of Model 2 in online supplementary table 1);
- (e) a sensitivity analysis where we additionally replaced HRs from the Oja et al.[18] study with the estimates from the Stamatakis et al.[19] study, that is, a subsequent analysis of the same data with further adjustments for social class and household income.

We also carried out the same sensitivity analyses as (d) and (e) above for CVD mortality. We assessed statistical heterogeneity of the HRs using the I^2 statistic, where I^2 values of 0%-40%, 30%-60%, 50%-90%, and 75%-100% were considered to represent low, moderate, substantial, and high heterogeneity, respectively.[47] We could not assess publication bias by using Egger’s asymmetry test due to the low number of included studies.[48]

The dose-response relationships from individual studies were pooled using a random-effects meta-regression analysis with Restricted Maximum Likelihood (REML) estimation. Prior to the meta-regression analysis of dose-response relationships, we harmonised the doses reported in individual studies. The doses that did not exactly match were harmonised according to the closest midpoint. This was done by one author (ZP) and checked for consistency and accuracy by another author (ST). If multiple studies from the same cohort presented data on dose-response relationships, we included in the meta-regression analysis the one that used the most detailed classification of dose. The categories of dose can be found in online supplementary table 2. We considered linear, quadratic, log-linear, and log-quadratic models when examining the dose-response curves. The model selection was based on the Akaike Information Criterion (AIC). The model with the smallest AIC statistic was considered to have the best balance between the simplicity and the goodness of fit. All analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria), using the ‘metafor’ package.[49]

RESULTS

Search and study selection results

The primary search resulted in a total of 19,315 references (figure 2). After removing 4,912 duplicates, we assessed 14,403 references against the inclusion criteria. Out of these, 13 publications[18, 30, 31, 44-46, 50-56] met all the inclusion criteria. Additionally, one eligible publication[19] was identified in the secondary search, from the reference lists of the included papers. This resulted in a total of 14 included publications, reporting results from the following cohort studies: the Aerobics Center Longitudinal Study (USA);[30, 46, 50] the Copenhagen City Heart Study (Denmark);[31, 44, 45, 56] the Health Survey for England and the Scottish Health

Survey (UK; hereinafter referred to as a single study, as their data were pooled);[18, 19] the National Health and Nutrition Examination Survey (USA);[54] the Shanghai Men’s Health Study (China);[51] and a cohort of runners from the 50+ Runners Association with controls from the Stanford University Lipid Research Clinics Prevalence Study (USA).[52, 53, 55]

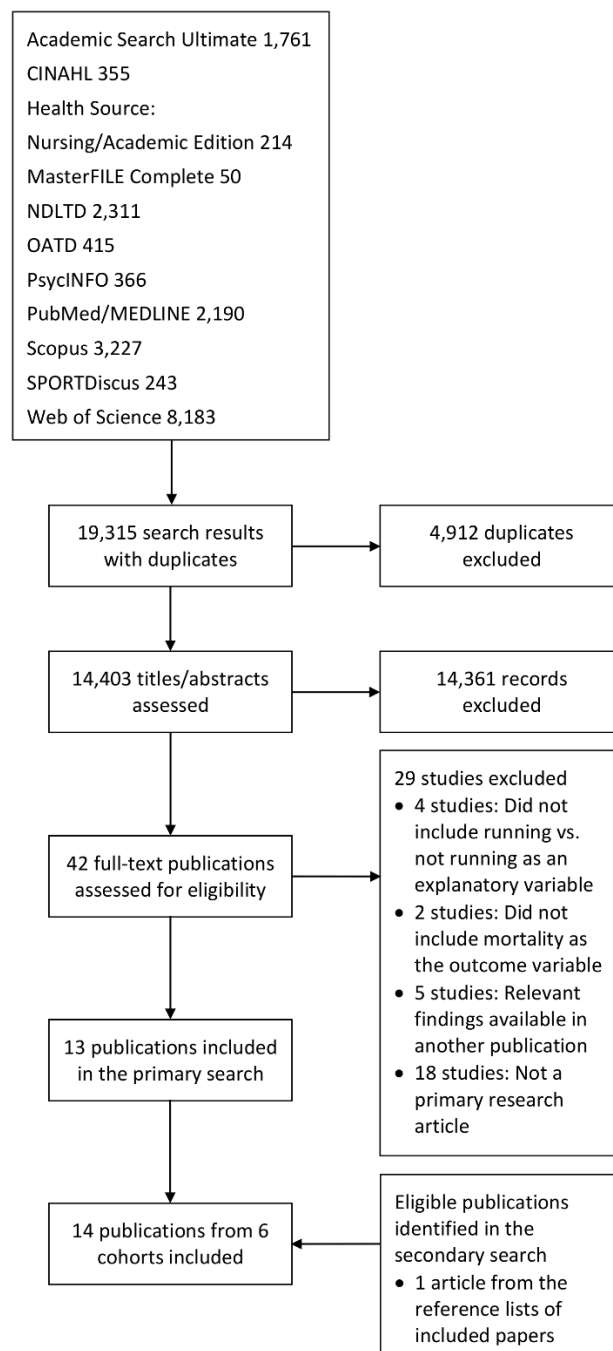


Figure 2 Flow diagram of the search and study selection process.

Study characteristics

The Wang et al.[51] study included only men, whilst the other studies included both sexes (online supplementary table 1). Four study samples were population-representative[18, 45, 51, 54], whilst the remaining two studies used convenience samples.[46, 55] The pooled sample size from the studies included in this review is 232,149, with individual study samples ranging from 961 to 80,306 participants. In all included studies, the data on running participation were collected using self-reports and the participants classified as runners (i.e. the exposure group) comprised around 10% of the pooled sample. The mortality data in all studies were obtained from national death registers, with the follow-up across individual studies ranging from 5.5 to 35 years. In total, 25,951 deaths were recorded in the study samples during follow-up.

Adjusted HRs suitable for the meta-analysis of the association between running participation and the risk of all-cause mortality were available from all cohorts except the National Health and Nutrition Examination Survey[54] (online supplementary table 1). Three studies reported adjusted HRs suitable for inclusion in the meta-analysis of the association between running participation and the risk of cardiovascular mortality.[18, 46, 51] Adjusted HRs suitable for the meta-analysis of the association between running participation and the risk of cancer mortality were available in three studies[30, 45, 51] and obtained upon request from the authors of one additional study.[18]

Findings on the relationship between the dose of running and the risk of all-cause mortality were available in five publications from three cohort studies (online supplementary table 2).[18, 30, 31, 45, 46] Analyses of dose-response relationships using the data from the Aerobics Center Longitudinal Study were conducted by Lee et al.[30, 46]. The Lee et al.[30] study includes a more

detailed classification of weekly duration, weekly frequency, and total volume of running. However, unlike in the Lee et al.[46] study, Lee et al.[30] did not analyse the relationship between running pace and mortality risk. Analyses of dose-response relationships from the Copenhagen City Heart Study data were conducted by Schnohr et al.[31, 45]. Schnohr et al.[31] study presented a more detailed analysis of the dose-response relationships. Furthermore, findings on the relationships between the dose of running and the risk of cardiovascular mortality were available in three publications from two cohort studies.[18, 30, 46] The relationship between the dose of running and the risk of cancer mortality was analysed in one study.[50]

The studies by Fries et al.,[52] Wang et al.,[53] and Schnohr et al.[56] were conducted using data from shorter follow-ups and with less death cases than subsequent, more recent studies from the respective cohorts.[45, 55] Furthermore, Schnohr et al.[44] was the most recent publication from the Copenhagen City Heart Study reporting the association between running and mortality. However, they included only participants of the third examination (1991-1994), which resulted in a shorter follow-up, a smaller sample size, and fewer number of deaths, when compared to a previous study from the same cohort.[45] Furthermore, in Stamatakis et al. study,[19] a large amount of missing data for the two additional variables included in the model (added on top of the original set of variables used in the Oja et al.[18] study) resulted in a significantly reduced sample size compared to the sample size in the original study.[18]

Methodological quality of the included studies

The included studies were given overall scores ranging from four to nine points out of the maximum of nine points on the NOS scale (online supplementary table 3). Based on the overall

scores, one study[55] was classified as being of “fair quality”, whilst all other studies were classified as being of “good quality”.

Adjustments for confounding

In regard to adjustments for confounding, models in the Oja et al.,[18] Stamatakis et al.,[19] Schnohr et al.,[45] and Wang et al.[51] studies, satisfied all the requirements for causal effect identification specified in figure 1. The other studies did not adjust for all the variables. For example, Chakravarty et al.[55] presented HRs adjusted for age, gender, and initial disability. Lee et al.[46] calculated HRs adjusted for age, sex, examination year, smoking status, alcohol consumption, other physical activities except running in one model and HRs adjusted for age, sex, examination year, smoking status, overweight/obesity, parental CVD, abnormal electrocardiogram, hypertension, diabetes, and hypercholesterolemia in another model.

Results of meta-analyses

Running participation and the risk of all-cause mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of all-cause mortality of 27% over the follow-up periods (figure 3; HR = 0.73; 95% confidence interval [CI]: 0.68, 0.79; $p < 0.001$). No significant heterogeneity in the effect sizes was found across the five studies ($I^2 = 8.54\%$). Similar results were obtained in all four sensitivity analyses (online supplementary figures 1-4).

A subgroup meta-analysis by sex showed similar results as the main analysis (online supplementary figures 5 and 6). The analysis for females and the analysis for males included HRs

available from two studies[45, 46] and three studies[45, 46, 51], respectively. The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of all-cause mortality of 34% for females (HR = 0.66; 95% CI: 0.52, 0.83; $p < 0.001$) and 27% for males (HR = 0.73; 95% CI: 0.67, 0.79; $p < 0.001$). No significant heterogeneity was found between the effect sizes from different studies ($I^2 < 0.001\%$ for both analyses).

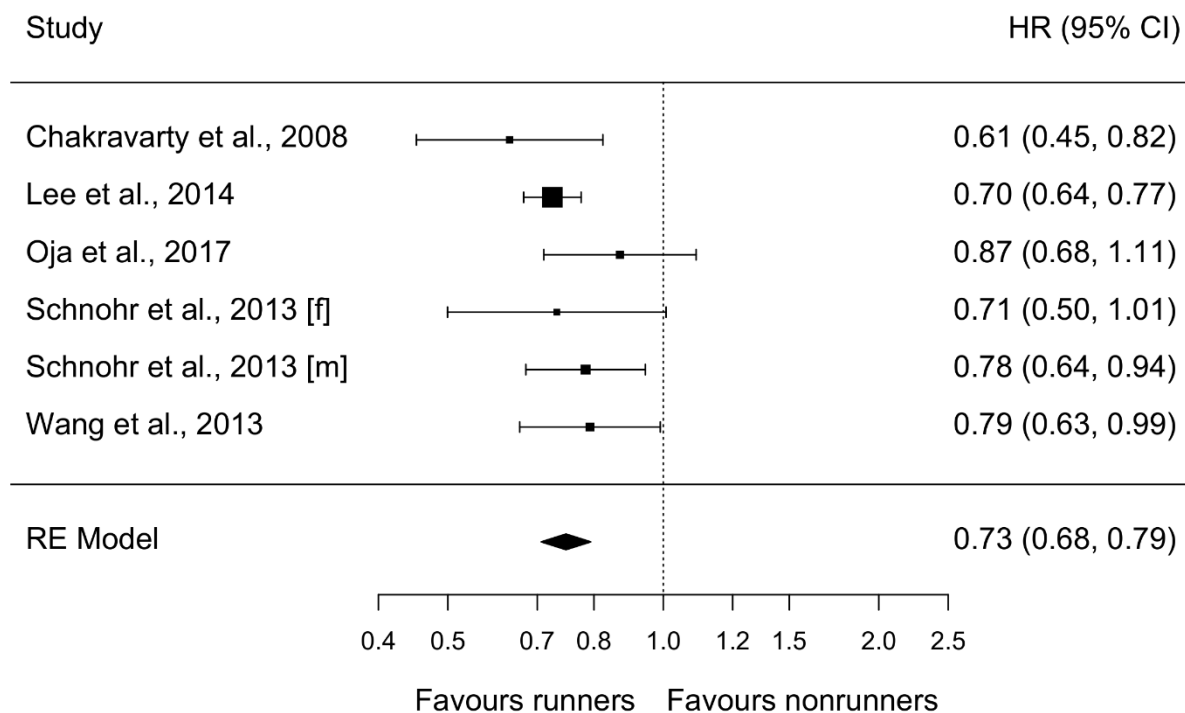


Figure 3 Running participation and all-cause mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; f, female subsample; m, male subsample; RE Model, pooled effect size from a random-effects meta-analysis model.

Running participation and the risk of cardiovascular mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of cardiovascular mortality of 30% over the follow-up periods (figure 4; HR = 0.70; 95% CI: 0.49, 0.98; $p = 0.040$). Substantial heterogeneity in the effect sizes was found across the three studies ($I^2 = 63.44\%$). Similar pooled HRs were obtained in both sensitivity analyses (online supplementary figures 7 and 8).

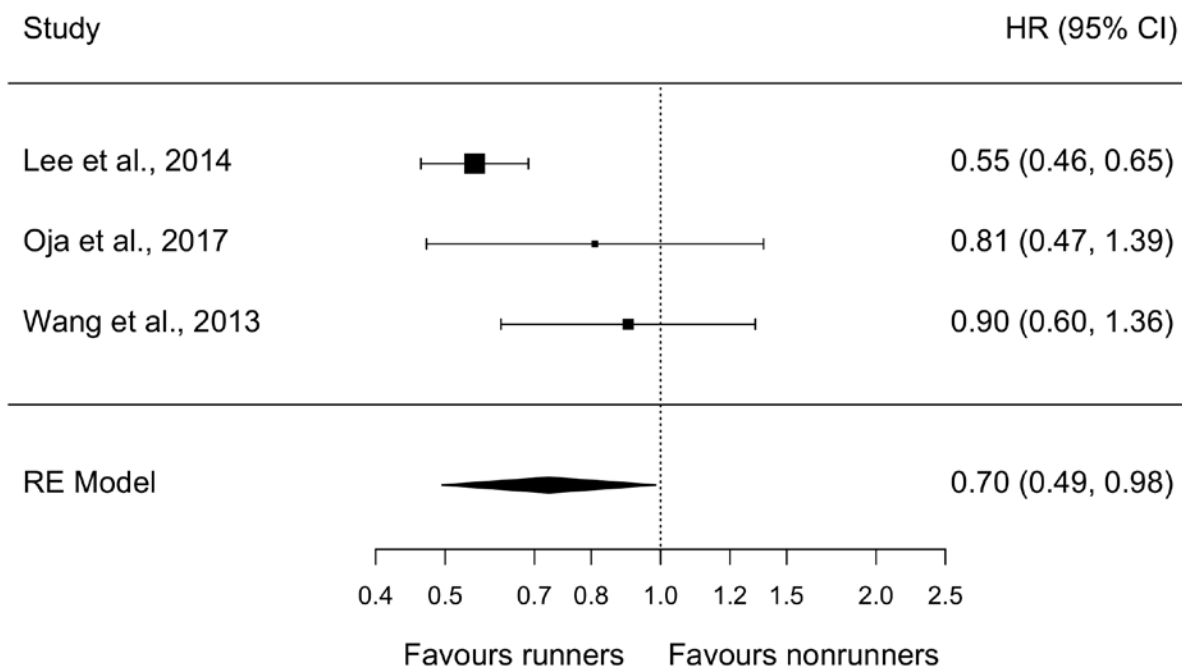


Figure 4 Running participation and cardiovascular mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; RE Model, pooled effect size from a random-effects meta-analysis model.

Running participation and the risk of cancer mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of cancer mortality of 23% over the follow-up periods (figure 5; HR = 0.77; 95% CI: 0.68, 0.87; $p < 0.001$). There was no significant heterogeneity between the effect sizes from the four individual studies ($I^2 < 0.001\%$).

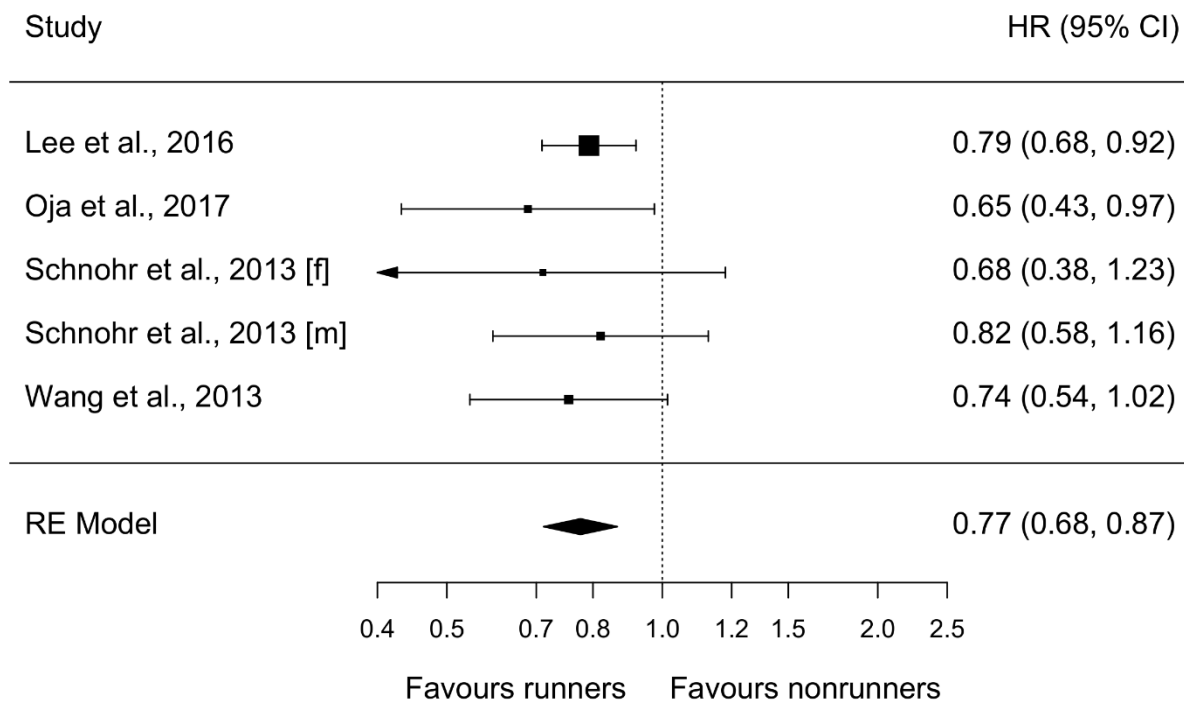


Figure 5 Running participation and cancer mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; f, female subsample; m, male subsample; RE Model, pooled effect size from a random-effects meta-analysis model; the meta-analysis included the adjusted HR from the study of Lee et al. [50].

Dose of running and the risk of mortality

We conducted meta-regression analyses only for the dose-response relationship between running and all-cause mortality (figure 6), because insufficient data from individual studies were available for cardiovascular and cancer mortality as outcome variables. In all four meta-regression analyses, the linear model had the lowest AIC value (12.36, 2.76, 7.41, and 13.95 in the analysis for frequency, duration, pace, and volume, respectively) compared to the other models. This suggested that the most parsimonious representation of the dose-response data was provided by a linear fit. However, no significant trends for dose response were found ($p > 0.05$ for all). There was moderate heterogeneity between the studies included in the meta-regression analyses for frequency, duration, and pace of running. The I^2 values were 47.62%, 32.88%, and 41.25%, respectively. We found substantial heterogeneity between the studies included in the meta-regression for the total volume of running ($I^2 = 62.57\%$). The meta-regression coefficients for the linear trend are presented in online supplementary table 4. They can be used to calculate the estimated pooled HR from the three analysed cohorts for a given dose of running. For example, the estimated pooled HR for the total volume of running of 675 MET-minutes/week (i.e., roughly equivalent to the recommended weekly minimum of MVPA[1]) is 0.68 (95% CI: 0.51, 0.78).

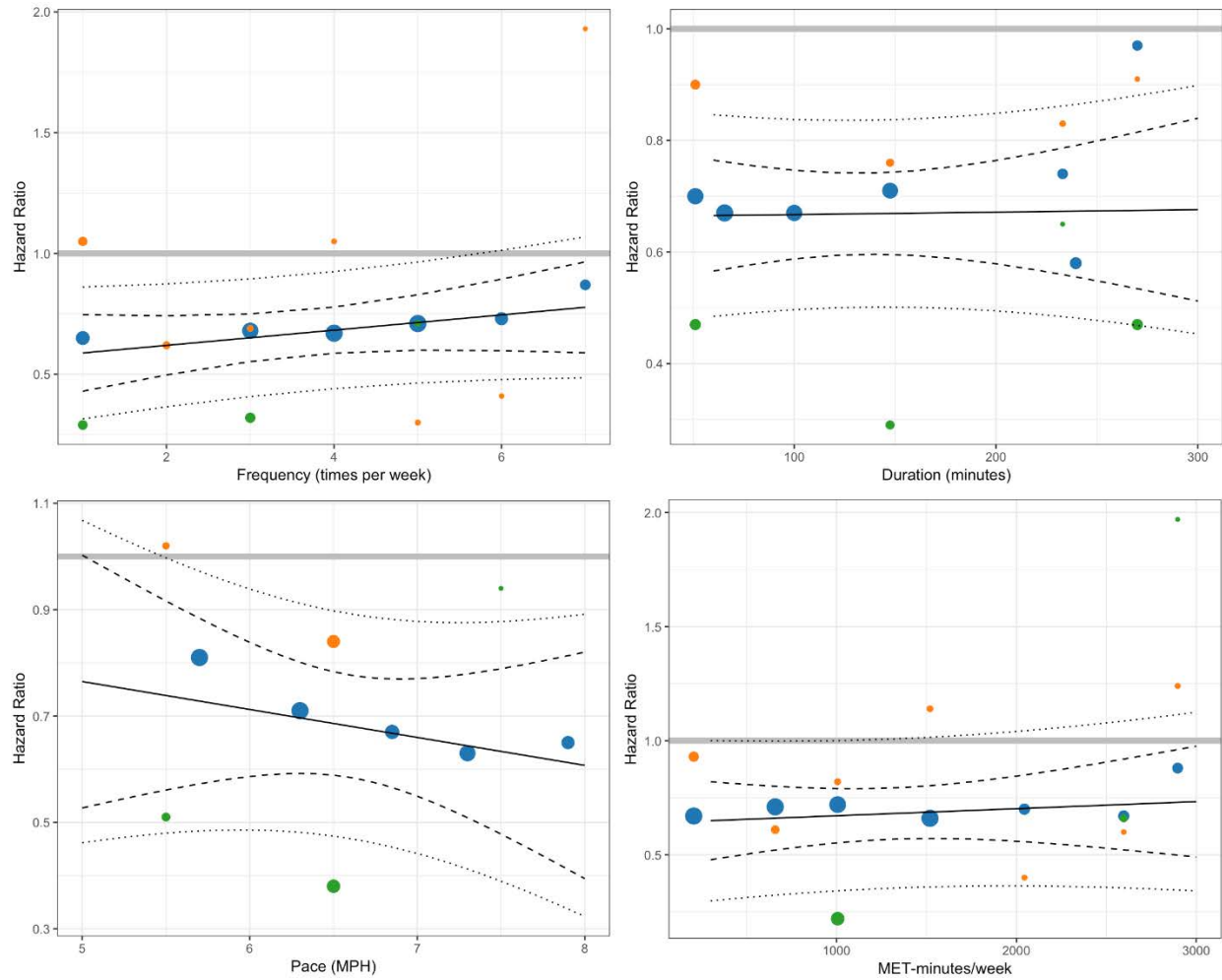


Figure 6 Dose of running and all-cause mortality risk: a meta-regression of hazard ratios. Blue circle, an adjusted hazard ratio (HR) from Lee et al. [46] for “pace” and Lee et al. [30] for “frequency”, “duration” and “volume”; orange circle, HR from Oja et al. [18] ; green circle, HR from Schnohr et al. [31]; The size of a circle is proportional to the precision of each study’s estimated HR at the specified dose.

DISCUSSION

Key findings

This systematic review synthesised results of fourteen studies from six prospective cohorts with a pooled sample of more than 230 thousand participants. The main finding is that running participation is associated with 27%, 30%, and 23% reduced risk of all-cause, cardiovascular, and cancer mortality, respectively. A meta-regression analysis combining results from three cohort studies revealed no significant dose-response trends. Even the smallest doses of running that were examined in the available studies (i.e. ≤ 1 time a week, < 50 minutes a week, < 6 mph, and < 500 MET-minutes/week) were found to confer significant all-cause mortality benefits. We found no evidence that mortality benefits increase with higher amounts of running.

Comparison with other studies

The systematic review by Oja and colleagues[17] included only one study on running participation and mortality risk. Two articles presented findings of more recent literature searches on health outcomes of running,[22, 57] but they were both narrative reviews and did not conduct meta-analyses to quantitatively estimate the pooled associations of running with health outcomes. To our knowledge, the current study is the first meta-analysis of the association between running participation and the risk of mortality.

A meta-analysis by Kelly and colleagues[21] found that 675 MET-minutes/week of walking and cycling (i.e., roughly equivalent to the current WHO MVPA recommendations[1]) is associated with a reduction in the risk of all-cause mortality by 11% (95% CI: 4%, 17%) and 10% (95% CI: 6%, 13%), respectively. In the sample of three cohort studies included in our meta-regression

analysis, we found that the same weekly volume of running conferred significantly greater mortality benefit (32%, 95% CI: 22%, 49%). However, the difference between mortality benefits for running, walking, and cycling seems to disappear at moderate and high total volumes of these activities. The ratios of metabolic rates of walking, cycling, and running to the resting metabolic rate (i.e. METs) vary significantly between and within individuals, depending greatly on the pace of activity.[58] We speculate that during short exercise/activity sessions, the intensity (expressed in METs) is on average higher for running than for walking and cycling. This would explain the observed difference between mortality benefits,[21] given that greater reductions in mortality risk are associated with participation in vigorous-intensity sports and exercise when compared to activities of lower intensities.[14] This finding warrants further research that would make direct comparisons between the associations of running, walking, and cycling with the risk of mortality in the same study sample(s).

A recent meta-analysis summarised the results of 35 running interventions (randomised controlled trials) among a total sample of more than 2,000 otherwise physically inactive adults.[59] Running roughly 3-4 times and 2-3 hours a week at the intensity of 60%-90% of the maximum heart rate for one year reduced body fat on average by 2.7%, resting heart rate by 6.7 beats per minute, and triglycerides by 16.9 mg/dL, whilst increasing the average maximal oxygen uptake (VO_{2max}) by 7.1 mL/min·kg and high-density lipoprotein (HDL) cholesterol by 3.3 mg/dL. These findings likely explain some of the underlying causal pathways linking running participation and lower mortality risk. In support of this notion, Lee et al.[46] found no association between running and mortality after adjusting for cardiorespiratory fitness. Although all studies in this review excluded participants with a history of severe illness at the baseline and/or adjusted their analysis for health

status, the possibility of reverse causation between running participation and health cannot be ruled out. In other words, the association between running and mortality may partially be explained by assuming that sick participants (who are more likely to die) were less likely to engage in running.

Implications for clinicians and policymakers

Some clinicians and public health stakeholders may have been discouraged from promoting running as a part of “lifestyle medicine” among their patients and communities, because vigorous exertion has been linked with sudden cardiac death.[60]. Our results provide meta-analytic evidence that, in the general population, the mortality benefit of running outweighs the risk. Previous studies suggested that this also holds true for some clinical populations.[22, 57] However, running might not be a suitable activity for all clinical populations, and a clinician may need to make an informed decision on whether or not to prescribe it on a case-by-case basis. Furthermore, participation in running is also associated with an increased injury risk, and the risk increases with increasing daily duration of the activity.[61] In cases when there is an increased risk of running-related overuse injuries,[62] clinicians may consider recommending walking or a lower dose of running. Our findings support such a recommendation by highlighting likely mortality benefits of low running doses.

The World Health Organization (WHO) guidelines and national physical activity recommendations in many countries (including the UK) suggest that adults should engage in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity a week.[1, 3] Seventy-five minutes per week of physical activity at the lower threshold for vigorous-

intensity (i.e. 6 METs) equals to 450 MET-minutes/week. Dose-response analyses from both the Aerobics Center Longitudinal Study[30] and the Health Survey for England/Scottish Health Survey[18] showed that even <506 MET-minutes/week of running are associated with a significant mortality benefit. These findings support the physical activity recommendation. However, >80% of runners seem to run at the pace faster than 6 mph,[46] which is associated with an energy cost of >9.8 METs.[58] This means that many runners could achieve mortality benefits with less than ~50 minutes a week, that is, in 25 minutes less than the recommended minimum amount of vigorous-intensity physical activity. This may be encouraging for people who struggle to find the time to exercise, given that a perceived lack of time has been consistently identified as a key barrier to physical activity participation.[63] Furthermore, the national physical activity recommendations in many countries suggest that more physical activity may confer additional health benefits, often referring to ≥ 300 minutes of moderate-intensity or ≥ 150 minutes of vigorous-intensity physical activity.[3] The results of our dose-response analysis do not support this recommendation in terms of running behaviour and mortality risk.

Strengths and limitations of the review and included studies

The key strength of this study was the rigorous methodological protocol, following PRISMA guidelines for systematic reviews.[41] We searched for eligible publications in a large number of bibliographic databases using broad search terms, which ensured that relevant studies were unlikely to be missed. Additionally, we contacted authors of three included studies[18, 45, 55] in an attempt to obtain unpublished data, and we obtained additional data from one study,[18] which has improved the comprehensiveness of our analyses. A limitation of this review is that, due to a small number of included studies, we could not assess publication bias. Moreover, one of the

included studies[54] reported a non-significant association between running participation and the risk of all-cause mortality, but it did not present results suitable for our meta-analysis. It might, therefore, be that the pooled HR for the association between running and mortality is somewhat overestimated.

All included studies were of good methodological quality, except for one study that was of fair quality. Despite their high scores on the methodological quality checklist, the studies had some limitations. First, although the analyses in all studies were adjusted for a range of variables, their results may have been affected by residual confounding. For example, one study[55] did not adjust for physical activities other than running. Higher physical activity levels are associated with a lower risk of mortality.[15] Not adjusting for this variable may have led to misestimation of the effects of running, that is, an overestimation, if physical activity other than running was higher among runners than among nonrunners, or an underestimation, if physical activity other than running was higher among nonrunners than among runners. It is worth noting that Chakravarty et al.[55] considered aerobic exercise as a covariate, but they decided not to include it in the final model, because it did not significantly alter the results. Only four studies[18, 19, 45, 51] satisfied all the requirements for causal effect identification specified in figure 1. However, it is possible that some causal relationships are in the opposite direction than those assumed in the DAG in figure 1. According to a less ‘conservative’ DAG (online supplementary figure 9), it would only be necessary to adjust for sociodemographic factors, unhealthy lifestyle, and health status. According to this ‘less conservative’ DAG, further adjustments for either adiposity or physical activity other than running would lead to over-adjustment. Second, the criteria for excluding participants in the included studies were usually limited to a history of cardiovascular disease or

cancer. Other diseases and debilitating conditions could prevent people from running whilst at the same time increasing their risk of dying prematurely. Third, results of some individual studies may have been affected by selection bias. For example, in one study,[55] the exposure group and the controls were not drawn from the same source, which was reflected in significant baseline differences between the groups. However, the exclusion of this study from the meta-analysis for all-cause mortality resulted in no significant change in the pooled HR. In the dose-response analysis from another study,[31] the reference group was defined as “sedentary nonrunners”. This might have led to an overestimation of mortality benefits of running, as it is likely that lower mortality rates in the exposure group were partially attributable to physical activity other than running. Due to the low number of studies that reported dose-response relationships, we could not conduct a sensitivity analysis by excluding this study. Fourth, although it generally seems that running is a relatively stable habit,[45] individuals may change their running behaviour over the years of follow-up. Only two included studies examined the association between persistence in running behaviour over time and mortality.[46, 56] Fifth, although distance is a potentially useful measure of running dose, it was assessed in one cohort study only.[46] Sixth, the included studies used self-reports to collect data on running participation. Potential issues with validity and reliability of such self-reported data[64] may have resulted in attenuated associations between running participation and mortality. It is reasonable to assume that the shape of the observed dose-response curves could have been affected by such limitations of the measurement. Besides, the questions about running varied across the cohorts, which may have reduced the between-study comparability of exposure data. Seventh, in the meta-analyses, we could not account for the fact that the weekly frequency, weekly duration, and pace of running were likely co-dependent. A future meta-analysis of individual-level data would be needed to address this issue.[65] Finally,

the number of participants in the included studies and, consequently, the precision of estimates tended to be lower for higher doses of running. Although our meta-regression accounted for the varying precision of estimates across doses, a larger number of participants with high doses of running would improve the pooled estimates.

Conclusions and recommendations for future research

Running participation is associated with a significantly lower risk of all-cause, cardiovascular, and cancer mortality, compared to no running. Any amount of running, even just once per week, is better than no running, whilst higher doses of running may not necessarily be associated with greater mortality benefits. Increased rates of participation in running, regardless of its dose, would likely lead to substantial improvements in population health and longevity.

More studies are needed to examine how sustained running behaviour over time, compared to sporadic participation in running, is associated with mortality risk. Future studies should also consider assessing running habits using activity trackers, as these devices have the potential to provide more detailed and accurate insights into running behaviour.

FOOTNOTES

Contributors ZP, PO, ES, ST, and AEB conceptualized the study. ZP wrote the study protocol. ZP conducted the literature searches. ZP and NS conducted the study selection and data extraction. NL and SJHB conducted the study quality assessment. JG assisted in solving discrepancies between duplicate study selections, data extractions, and quality assessments. SK conducted the meta-regression analysis. ZP conducted the other meta-analyses and created directed acyclic

graphs. ZP and NS drafted the methods section of the manuscript. ZP drafted all other sections of the manuscript. All authors critically revised the draft manuscript and contributed to the subsequent revisions and the final version of the manuscript.

Funding The authors declare no sources of funding for this study.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary file 1 Search syntax

EBSCOHost (including Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, PsycINFO, and SPORTDiscus)

(running OR jogging OR runner* OR jogger*) AND (mortalit* OR death* OR fatal*)

Networked Digital Library of Theses and Dissertations (NDLTD)

(running OR jogging OR runner* OR jogger*) AND (mortalit* OR death* OR fatal*)

Open Access Theses and Dissertations (OATD)

(running OR jogging OR runner* OR jogger*) AND (mortalit* OR death* OR fatal*)

PubMed/MEDLINE

(running[TW] OR jogging[TW] OR runner*[TW] OR jogger*[TW]) AND (mortalit*[TW] OR death*[TW] OR fatal*[TW])

Scopus

title-abs-key(running OR jogging OR runner* OR jogger*) AND title-abs-key (mortalit* OR death* OR fatal*)

Web of Science (including Science Citation Index Expanded - SCI-EXPANDED, Social Sciences Citation Index - SSCI, Arts & Humanities Citation Index - A&HCI, Conference Proceedings Citation Index- Science - CPCI-S, and Conference Proceedings Citation Index- Social Science & Humanities - CPCI-SSH)

TS=(running OR jogging OR runner* OR jogger*) AND TS=(mortalit* OR death* OR fatal*)

Supplementary file 2 Differences from the registered protocol

The review protocol has been registered in the International Prospective Register of Systematic Reviews – PROSPERO (registration id: CRD42016049965). In the registered protocol, the search was limited to the documents published from 2013 onwards, given that a previous review on a similar topic was planned to be used as a reference point. However, based on a suggestion from a reviewer, while revising the manuscript we decided to conduct the search without a time limit. Furthermore, in the registered protocol the search was planned to be done in Academic Search Premier and MasterFILE Premier (among other databases). However, in the updated search we used Academic Search Ultimate and MasterFILE Complete; larger variants of the two bibliographic databases, because our university library in the meantime expanded its subscription to these larger databases, and we could not access Academic Search Premier and MasterFILE Premier anymore.

Supplementary table 1 Summary of studies on the association between running participation and the risk of all-cause, cardiovascular, and cancer mortality

Cohort	Study and location	Sample	Age at baseline <i>Mean±SD</i> <i>years</i>	Follow-up	Person-Years	Number of runners in the sample	Number of non-runners in the sample	Number of death events	Assessment of running	Outcome assessment	Adjustment for confounding variables	Data analysis method	Summary results <i>Hazard ratios (HR) from adjusted models (if not stated otherwise)</i>	Dose-response analysis
Runners from the 50+ Runners Association with controls from the Stanford University Lipid Research Clinics Prevalence Study	Fries et al. (1994), USA (Northern Carolina)	Exposure group: members of a nationwide runners club aged ≥ 50 years (n = 451, 83% males); Controls: permanent university staff and faculty between 50 and 72 years of age recruited from the roster of the Stanford University Lipid Research Clinics Prevalence Study (n = 330, 56% males)	Exposure group: 58±5.7; Controls: 61±7.1	8 years	n/a	Exposure group: n = 451; Total number of runners (across both groups): n = 534	Controls: n = 330; Total number of non-runners: n = 247	Whole sample: 38 (all-cause), 11 (CVD); Exposure group: 8 (all-cause), 1 (CVD); Controls: 30 (all-cause), 10 (CVD)	Membership in a running club; Self-administered questionnaire ("Have you ever run for exercise for a period of greater than 1 month?")	National Death Index	Baseline age, initial disability assessed by Health Assessment Questionnaire Disability Index (HAQ-DI), educational level, smoking, body mass index, history of arthritis, and comorbid conditions	Cox proportional hazards model (only for all-cause mortality)	All-cause mortality: HR = 0.23 (95% CI: 0.10, 0.56)	n/a
	Wang et al. (2002), USA (Northern Carolina)	Exposure group: members of a nationwide runners club aged ≥ 50 years (n = 538, 82% males); Controls: permanent university staff and faculty between 50 and 72 years of age recruited from the roster of the Stanford University Lipid Research Clinics Prevalence Study (n = 423, 56% males)	Exposure group: 58±5.2; Controls: 61±6.5	13 years	12,493	Exposure group: n = 538	Controls: n = 423	Whole sample: 93 (all-cause), 28 (CVD), 35 (cancer); Exposure group: 26 (all-cause), 9 (CVD), 11 (cancer); Controls: 67 (all-cause), 19 (CVD), 24 (cancer)	Membership in a running club; Self-administered questionnaire ("Have you ever run for exercise for a period of greater than 1 month?")	National Death Index	Baseline age, sex, weekly time spent in aerobic exercise other than running, and smoking, BMI and alcohol consumption were considered but were not included in the final model based on "statistical grounds".	Cox proportional hazards model; Rate ratios expressed per 100,000 person-years (HRs only available for all-cause mortality)	All-cause mortality: HR = 0.36 (95% CI: 0.20, 0.65), rate ratio = 3.28 (no p-value reported); CVD mortality: rate ratio = 2.68 (p = 0.55); Cancer mortality: rate ratio = 2.77 (p = 0.56)	n/a
	Chakravarty et al. (2008), USA (Northern Carolina)	Exposure group: members of a nationwide runners club aged ≥ 50 years (n = 538, 84% males); Controls: permanent university staff and faculty between 50 and 70 years of age recruited from the roster of the Stanford University Lipid Research Clinics Prevalence Study (n = 423, 56% males)	Exposure group: 58±5.6; Controls: 62±7.2	19 years	17,201	Exposure group: n = 538; Total number of runners (across both groups): n = 681	Controls: n = 423; Total number of non-runners: n = 280	Whole sample: 225 (all-cause), 72 (CVD), 71 (cancer); Exposure group: 81 (all-cause), 29 (CVD), 30 (cancer); Controls: 144 (all-cause), 43 (CVD), 41 (cancer)	Membership in a running club; Self-administered questionnaire ("Have you ever run for exercise for a period of greater than 1 month?")	National Death Index	Baseline age, gender, and initial disability assessed by Health Assessment Questionnaire Disability Index (HAQ-DI). Although initially considered as covariates, BMI, smoking history, and weekly aerobic exercise at baseline "did not meet statistical significance to be included in the final model".	Cox proportional hazards model; Unadjusted rate ratios expressed per 100,000 person-years (adjusted HRs only available for all-cause mortality)	All-cause mortality: HR = 0.61 (95% CI: 0.45, 0.82), rate ratio = 2.5 (p < 0.001); CVD mortality: rate ratio = 2.1 (p = 0.001); Cancer mortality: rate ratio = 1.9 (p = 0.004)	n/a

Aerobics Center Longitudinal Study	Lee et al. (2014, 2016a, 2016b), USA (Texas)	Participants were 18-100 years old adults referred for periodic preventive medical examination at a clinic in Dallas, Texas (n = 55,137 for all-cause mortality analysis, 52,941 for CVD mortality analysis, 52,917 for cancer mortality analysis, 74% males). Those reporting myocardial infarction, stroke or cancer at baseline, and those who died within less than 1 year of follow up were excluded from analyses.	Runners Q1: 40±9; Runners Q2: 41±9; Runners Q3: 42±9; Runners Q4: 42±9; Runners Q5: 43±9; Non-runners: 45±11	14.7 years (mean for all-cause mortality sample); 14.6 (mean for CVD and cancer mortality samples)	827,055	n = 13,016 (all-cause mortality analysis); n = 12,622 (CVD mortality analysis); n ≈ 12,700 (cancer mortality analysis)	n = 42,121 (All-cause mortality analysis); n = 40,319 (CVD mortality analysis); n ≈ 40,217 (cancer mortality analysis)	Whole sample: 3,413 (all-cause), 1,217 (CVD), 1,193 (cancer); Runners: 556 (all-cause), 162 (CVD); Non-runners: 2,857 (all-cause), 1,055 (CVD)	Self-reported running or jogging activity over the past 3 months, including data about duration, distance, frequency and speed (assessed at two medical examinations; in 1974 and 2002)	National Death Index	In Model 1: baseline age, sex, examination year, smoking status, alcohol consumption, other physical activities except running (0, 1-499 MET-min/wk, ≥500 MET-min/wk), and parental CVD (except in cancer mortality analysis) In Model 2: baseline age, sex, examination year, smoking status, overweight/obesity based on body mass index, parental CVD, abnormal electrocardiogram, hypertension, diabetes, hypercholesterolemia	Cox proportional hazards model	Model 1: All-cause mortality: HR(total) = 0.70 (95% CI: 0.64, 0.77), HR(males) = 0.71 (95% CI: 0.64, 0.78), HR(females) = 0.61 (95% CI: 0.45, 0.85); CVD mortality: HR = 0.55 (95% CI: 0.46, 0.65), HR(males) = 0.56 (95% CI: 0.47, 0.67), HR(females) = 0.32 (95% CI: 0.16, 0.64); Cancer mortality: HR(total) = 0.79 (95% CI: 0.68, 0.92) Model 2: All-cause mortality: HR = 0.81 (95% CI: 0.73, 0.88), CVD mortality: HR = 0.71 (95% CI: 0.60, 0.85)	In Lee et al. (2014), HRs and their 95% CIs for all-cause and CVD mortality available for quintiles of running time, running distance, weekly frequency, running speed, and total volume of running. In Lee et al. (2016a), HRs and their 95% CIs for all-cause and CVD mortality available for groups by running time in minutes/wk (0, <51, 51-80, 81-119, 120-175, 176-209, 210-269, and ≥270), running distance in miles/wk (0, <6, 6-8, 9-12, 13-19, 20-23, 24-30, ≥31), weekly frequency of running (0, 1-2, 3, 4, 5, 6, ≥7), and total amount of running in MET-minutes/wk (0, <506, 506-812, 813-1199, 1200-1839, 1840-2249, 2250-2943, ≥2944). These represent non-runners (first group), the first four quintiles (second to fifth group), and three tertiles of the last quintile (sixth to eighth group), except for weekly frequency of running that includes 7 groups. In Lee et al. (2016b), HRs and their 95% CIs for cancer mortality available for quintiles of running time, running distance, weekly frequency, and total volume of running. The results are summarised in Supplementary table 2.
National Health and Nutrition Examination Survey	Loprinzi (2015), USA	Participants were 18-85 years old adults who participated in NHANES 1999-2006 surveys (n = 16,049, 49% males). Those with self-reported physician-diagnosed congestive heart failure, coronary artery disease, heart attack, stroke, emphysema, or bronchitis were excluded from analyses.	43 (standard deviation not available)	8.7 years (mean follow-up)	n/a	n = 358 (≥2000 MET-min/month of jogging); n = 698 (≥2000 MET-min/month of running)	n = 15,691 (<2000 MET-min/month of jogging); n = 15,351 (<2000 MET-min/month of running)	Whole sample: 1,290; data not available for joggers and runners	Self-reported running and jogging over the past 30 days, including data about duration and frequency. Exposure variables were binary variables including the categories "≥2000 MET-min/month" and <2000 MET-min/month for running and jogging. Data collected using face-to-face interviews.	National Death Index	Baseline age, gender, race-ethnicity, body mass index, total moderate-to-vigorous physical activity (MET-min/month), and binary variables including the categories "≥2000 MET-min/month" and <2000 MET-min/month for the following activities: aerobics; basketball; bicycling; dance; stair climbing; swimming; walking; and weight lifting	Cox proportional hazards model	≥2000 MET-min/month of jogging and ≥2000 MET-min/month of running were not significantly associated with the risk of all-cause mortality (results not shown in the paper)	n/a

Health Survey for England and the Scottish Health Survey	Oja et al. (2017), Stamatakis et al. (2017), United Kingdom (England and Scotland)	<p>Participants were 30-98 years old adults from the population-representative Health Survey from England and Scottish Health Survey (n = 80,306 for all-cause mortality analysis and 75,014 for CVD mortality analysis, 46% males). Those reporting doctor-diagnosed CVD at baseline were excluded from the analyses on CVD mortality. In a sensitivity analysis participants who died in the first 24 months of follow-up were excluded.</p> <p>In a subsequent sensitivity analysis, Stamatakis et al. (2017), due to missing income data, 35% of the full sample was excluded (n = 52,031 for the all-cause mortality analysis and n = 48,965 for the CVD mortality analysis).</p>	51.9±14.5 years	9.2±4.3 years (mean±SD)	736,463	<p>n = 4,012 (all-cause mortality analysis); n = 3,988 (CVD mortality analysis)</p> <p>In the subsequent sensitivity analysis: n = 2857 (all-cause mortality analysis); n = 2,840 (CVD mortality analysis)</p>	<p>n = 76,294 (All-cause mortality analysis); n = 71,026 (CVD mortality analysis)</p> <p>In the subsequent sensitivity analysis: n = 49,174 (all-cause mortality analysis); n = 46,125 (CVD mortality analysis)</p>	<p>Whole sample: 8,790 (all-cause), 1909 (CVD); Runners: 68 (all-cause), 13 (CVD); Non-runners: 8,722 (all-cause), 1,896 (CVD)</p> <p>In the subsequent sensitivity analysis - Whole sample: data not shown; Runners: 36 (all-cause), 5 (CVD); Non-runners: data not shown</p>	Self-reported running over the past 4 weeks. Face-to-face interviews conducted using the Physical Activity and Sedentary Behaviour Assessment Questionnaire (PASBAQ).	British National Health Service (NHS) Central Registry	<p>Baseline age, sex, long-standing illness, alcohol drinking frequency, psychological distress, BMI, smoking status, education level, doctor-diagnosed cancer, and weekly volume of other physical activity in MET-hours/week. The all-cause mortality analysis was also additionally adjusted for doctor-diagnosed CVD.</p> <p>In the subsequent sensitivity analyses additionally adjusted for occupational social class and household income.</p>	Cox proportional hazards model	<p>All-cause mortality: HR(total) = 0.87 (95% CI: 0.68, 1.11); CVD mortality: HR = 0.81 (95% CI: 0.47, 1.39); Cancer mortality: HR = 0.65 (95% CI: 0.43, 0.97)</p> <p>In the subsequent sensitivity analysis - HR(total) = 1.06 (95% CI: 0.76, 1.48); CVD mortality: HR = 0.84 (95% CI: 0.34, 2.04).</p>	<p>HRs and their 95% CIs for all-cause and CVD mortality are available for intensity ('Lower', 'Higher'), weekly duration ('Low', 'High'), and weekly volume ('Low', 'High') categories. Low and high intensity, respectively, were defined as answering "no" or "yes" to the question: "Was the effort of [(name of activity)] usually enough to make you out of breath or sweaty?". Low/high weekly duration and volume were defined using median split. Additional results for more detailed categorisations of running doses were obtained upon request from the authors.</p> <p>The results are summarised in Supplementary table 2.</p>
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Copenhagen City Heart Study	Schnohr et al. (2000), Denmark (Copenhagen)	Participants were 20-79 years old adults randomly selected from the Copenhagen Population Register (n = 4,658), who attended two examinations (1976-1978 and 1981-1983). Those with a history of myocardial infarction were excluded from the original sample.	n/a	17-22 years (range)	n/a	Runners in at least one survey year n = 323; Runners in both survey years ("persistent runners") n = 96	Non-runners in at least one survey year n = 4,562; Non-runners in both survey years n = 4,335	n/a	Self-reported participation in jogging or competitive running (general question "Are you a jogger or competition runner?")	National Central Person Register and National Register of Causes of Death	Baseline age, diabetes, smoking household income, education, alcohol consumption, systolic blood pressure, concentration of plasma total cholesterol, concentration of plasma high density lipoprotein cholesterol, and body mass index	Cox proportional hazards model	Significant association with the risk of all-cause mortality only found for "persistent runners": HR = 0.39 (95% CI: 0.19, 0.73)	n/a
	Schnohr et al. (2013), Denmark (Copenhagen)	Participants were 20-98 years old adults randomly selected from the Copenhagen Population Register (n = 18,219; 47% males). Those with a history of coronary heart disease, stroke, and/or cancer were excluded from the original sample.	Male runners: 36.4±12.1 years; Male non-runners: 51.0±13.0 years; Female runners: 33.3±10.4 years; Female non-runners: 50.4±13.0 years	8-35 years (range)	n/a	Males n = 1,089; Females n = 741 (all-cause mortality analysis); Males n = 1,098; Females n = 745 (coronary heart disease mortality, stroke mortality and cancer mortality analyses)	Males n = 7,398 and females n = 8,737 (all-cause mortality analysis); Males n = 7,501 and females n = 8,875 (coronary heart disease mortality, stroke mortality and cancer mortality analyses)	Males n = 4,934 and females n = 4,878 (whole sample in all-cause mortality analysis); Males n = 91 and females n = 26 (sample of runners in all-cause mortality analysis); Males n = 4,843 and females n = 4,852 (sample of non-runners in all-cause mortality analysis)	Self-reported participation in jogging or competitive running (general question "Are you a jogger or competition runner?")	National Central Person Register and National Register of Causes of Death	Baseline age, education, income, smoking, alcohol drinking habits, diabetes mellitus (coronary heart disease mortality, stroke mortality, cancer mortality, dose-response analyses) + leisure-time physical activity, resting heart rate, cholesterol, body mass index, systolic blood pressure, and the use of antihypertensive drugs (all-cause mortality analysis)	Cox proportional hazards model	All-cause mortality: HR(males) = 0.78 (95% CI: 0.64, 0.94), HR(females) = 0.71 (95% CI: 0.50, 1.01); Coronary heart disease mortality: HR(males) = 0.32 (95% CI: 0.15, 0.67), HR(females) = 0.48 (95% CI: 0.12, 1.96); Stroke mortality: HR(males) = 0.95 (95% CI: 0.42, 2.18), HR(females) = 0.85 (95% CI: 0.21, 3.42); Cancer mortality: HR(males) = 0.82 (95% CI: 0.58, 1.16), HR(females) = 0.68 (95% CI: 0.38, 1.23)	HRs and their 95% CIs for all-cause mortality are available for groups by weekly duration, weekly frequency, and pace of running. The analysis included participants who participated in the second, third, and fourth surveys.
	Schnohr et al. (2015), Denmark (Copenhagen)	Participants were 20-92 years old adults randomly selected from the Copenhagen Population Register who participated in the fourth examination, 2001-2003 (n = 1,511; 51% males). Those with a history of coronary heart disease, stroke, and/or cancer were excluded from the original sample.	Runners: 42.5 (standard deviation not available); "Sedentary" non-runners: 61.3±16.2	12 years	n/a	n = 1,098	n = 413 (defined as "sedentary" non-runners)	Whole sample: n = 128; Sample of runners n = 28; Sample of "sedentary" non-runners n = 100	Self-reported weekly quantity, frequency, and pace (slow, average, fast) of running	National Central Person Register	Baseline age, sex, smoking, alcohol intake, education, and diabetes mellitus	Cox proportional hazards model	No results are available for the association between overall running participation and mortality. The results from dose-response analyses are summarised in Supplementary table 2.	HRs and their 95% CIs for all-cause mortality are available for groups by weekly duration of running (<1 hour, 1-2.4 hours, 2.5-4 hours, >4 hours), weekly frequency of running (≤1 time, 2-3 times, >3 times), running pace (slow, average, fast) and overall "dose" of running (light jogger, moderate jogger, strenuous jogger). "Sedentary" non-runners (not all non-runners) were used as the reference group. The results are summarised in Supplementary table 2.
	Schnohr et al. (2018), Denmark (Copenhagen)	Participants were 20+ years old adults randomly selected from the Copenhagen Population Register who participated in the third examination, 1991-1994 (n = 1,325; 51% males). Those with a history of coronary heart disease, stroke, cancer, and/or missing information about leisure-time physical activity were excluded from the original sample.	Runners: 40±12; "Sedentary" non-runners: 61±15	25 years	n/a	n = 309	n = 926 (defined as "sedentary" non-runners)	Whole sample: n = 693; Sample of runners n = 64; Sample of "sedentary" non-runners n = 629	Self-reported participation in jogging	National Central Person Register	Baseline age, sex, weekly volume of overall leisure-time physical activity, smoking, education, income, alcohol intake, and diabetes mellitus	Cox proportional hazards model	All-cause mortality: HR = 0.72 (95% CI: 0.55, 0.94);	n/a

Shanghai Men's Health Study	Wang et al. (2013), China (Shanghai)	Participants were 40-74 years old men recruited from 2002-2006 from urban communities in Shanghai, China (n = 61,477). Those with previously diagnosed cancer were excluded from the analyses. A sensitivity analysis was performed on participants without a history of CVD at baseline and who did not die within the first year of follow-up (n = 50,505).	55.4 years (standard deviation not available)	5.5 years (mean)	336,894	3,214	58,263	<p>Whole sample: 2,421 (all-cause), 800 (CVD), 1053 (cancer); Runners: 99 (all-cause), 33 (CVD), 44 (cancer); Non-runners: 2,322 (all-cause), 767 (CVD), 1,009 (cancer)</p> <p>In the sensitivity analysis - Whole sample: 1,784 (all-cause), 473 (CVD), 892 (cancer); Runners: 85 (all-cause), 26 (CVD), 42 (cancer); Non-runners: 1,699 (all-cause), 447 (CVD), 850 (cancer)</p>	Self-reported participation in jogging or running for exercise in the past 5 years. Face-to-face interviews conducted using the Shanghai Men's Health Study Physical Activity Questionnaire	Through biennial in-home surveys and data linkage to the Shanghai Cancer Registry and the Shanghai Vital Statistics Registry	Baseline age, educational level, income, occupation (professional, clerical, manual workers), cigarette smoking, alcohol intake, daily physical activity other than exercise, participation in exercise other than jogging, body mass index, history of CVD, chronic liver disease, diabetes, hypertension, and pulmonary disease, total energy intake, intake of red meat, intake of vegetables and fruit intake.	Cox proportional hazards model	<p>All-cause mortality: HR = 0.73 (95% CI: 0.59, 0.90); CVD mortality: HR = 0.74 (95% CI: 0.52, 1.06); Cancer mortality: HR = 0.69 (95% CI: 0.51, 0.94).</p> <p>In the sensitivity analysis - All-cause mortality: HR = 0.79 (95% CI: 0.63, 0.99); CVD mortality: HR = 0.90 (95% CI: 0.60, 1.36); Cancer mortality: HR = 0.74 (95% CI: 0.54, 1.02)</p>	n/a
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Lee et al (2016a) = reference number 30; Lee et al (2016b) = reference number 50

Supplementary table 2 Summary results of the studies on the dose-response relationship between running and the risk of all-cause mortality

Dose type	Lee et al. (2014; pace), Lee et al. (2016; other variables)		Schnohr et al. (2015)		Oja et al. (2017)	
	Category	HR (95% CI)	Category	HR (95% CI)	Category	HR (95% CI)
Duration	<51 min/week	0.70 (0.58, 0.85)	< 1 hour/week	0.47 (0.29, 0.77)	<51 min/week	0.93 (0.67, 1.28)
	51-80 min/week	0.67 (0.55, 0.80)	1-2.4 hours/week	0.29 (0.11, 0.80)	51-80 min/week	0.75 (0.39, 1.44)
	81-119 min/week	0.67 (0.55, 0.82)			81-119 min/week	0.58 (0.22, 1.55)
	120-175 min/week	0.71 (0.58, 0.86)			120-175 min/week	1.18 (0.61, 2.28)
	176-209 min/week	0.74 (0.52, 1.04)	2.5-4 hours/week	0.65 (0.20, 2.07)	176-209 min/week	0.75 (0.19, 3.02)
	210-269 min/week	0.58 (0.40, 0.83)			210-269 min/week	0.38 (0.05, 2.73)
	≥270 min/week	0.97 (0.73, 1.27)	> 4 hours/week	0.60 (0.08, 4.36)	≥270 min/week	0.92 (0.38, 2.21)
Frequency	1-2 times per week	0.65 (0.51, 0.84)	≤1 time	0.29 (0.12, 0.72)	≤1 time per week	1.05 (0.77, 1.42)
	3 times per week	0.68 (0.56, 0.82)	2-3 times	0.32 (0.15, 0.69)	2 times per week	0.62 (0.31, 1.25)
					3 times per week	0.69 (0.29, 1.65)
	4 times per week	0.67 (0.56, 0.80)	>3 times	0.71 (0.29, 1.75)	4 times per week	1.05 (0.39, 2.81)
	5 times per week	0.71 (0.60, 0.84)			5 times per week	0.30 (0.04, 2.12)
	6 times per week	0.73 (0.57, 0.93)			6 times per week	0.41 (0.06, 2.92)
	7+ times per week	0.87 (0.65, 1.15)			7+ times per week	1.93 (0.92, 4.05)
Pace/speed	<6 mph	0.81 (0.66, 0.97)	Slow (<6 mph)	0.51 (0.24, 1.10)	Lower perceived intensity (<6 mph)	1.02 (0.59, 1.78)
	6-6.6 mph	0.71 (0.56, 0.87)	Average (6-7 mph)	0.38 (0.22, 0.66)	Higher perceived intensity (≥6 mph)	0.84 (0.64, 1.10)
	6.7-7 mph	0.67 (0.47, 0.87)				
	7.1-7.5 mph	0.63 (0.46, 0.80)	Fast (>7 mph)	0.94 (0.40, 2.18)		
	≥7.6 mph	0.65 (0.43, 0.88)				
Total volume	<506 MET-min/week	0.67 (0.55, 0.81)	"Light" runners, <1800 MET-min/week	0.22 (0.10, 0.47)	<506 MET-min/week	0.93 (0.68, 1.28)
	506-812 MET-min/week	0.71 (0.59, 0.85)			506-812 MET-min/week	0.61 (0.32, 1.17)
	813-1199 MET-min/week	0.72 (0.60, 0.87)			813-1199 MET-min/week	0.82 (0.34, 1.98)
	1200-1839 MET-min/week	0.66 (0.54, 0.80)			1200-1839 MET-min/week	1.14 (0.57, 2.28)
	1840-2249 MET-min/week	0.70 (0.49, 0.99)	"Moderate" runners, 1800 - 2880 MET-min/week	0.66 (0.32, 1.38)	1840-2249 MET-min/week	0.40 (0.06, 2.83)
	2250-2943 MET-min/week	0.67 (0.46, 0.96)			2250-2943 MET-min/week	0.60 (0.08, 4.23)
	≥2944 MET-min/week	0.88 (0.65, 1.19)	"Strenuous" runners, >2880 MET-min/week	1.97 (0.48, 8.14)	≥2944 MET-min/week	1.24 (0.46, 3.30)

Lee et al (2016) = reference number 30

Supplementary table 3 Methodological quality appraisal using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Assessment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Ascertainment of outcome	Long enough follow-up for outcomes to occur	Adequacy of follow-up of cohorts	Overall score
Fries et al. (1994); Wang et al. (2002); Chakravarty et al. (2008)	-	-	-	-	**	*	*	-	4
Lee et al. (2014, 2016a, 2016b)	*	*	-	*	**	*	*	-	7
Loprinzi (2015)	*	*	*	*	**	*	*	*	9
Oja et al. (2017); Stamatakis et al. (2017)	*	*	*	*	**	*	*	*	9
Schnohr et al. (2000, 2013, 2015, 2018)	*	*	-	*	**	*	*	*	8
Wang et al. (2013)	*	*	*	*	**	*	*	*	9

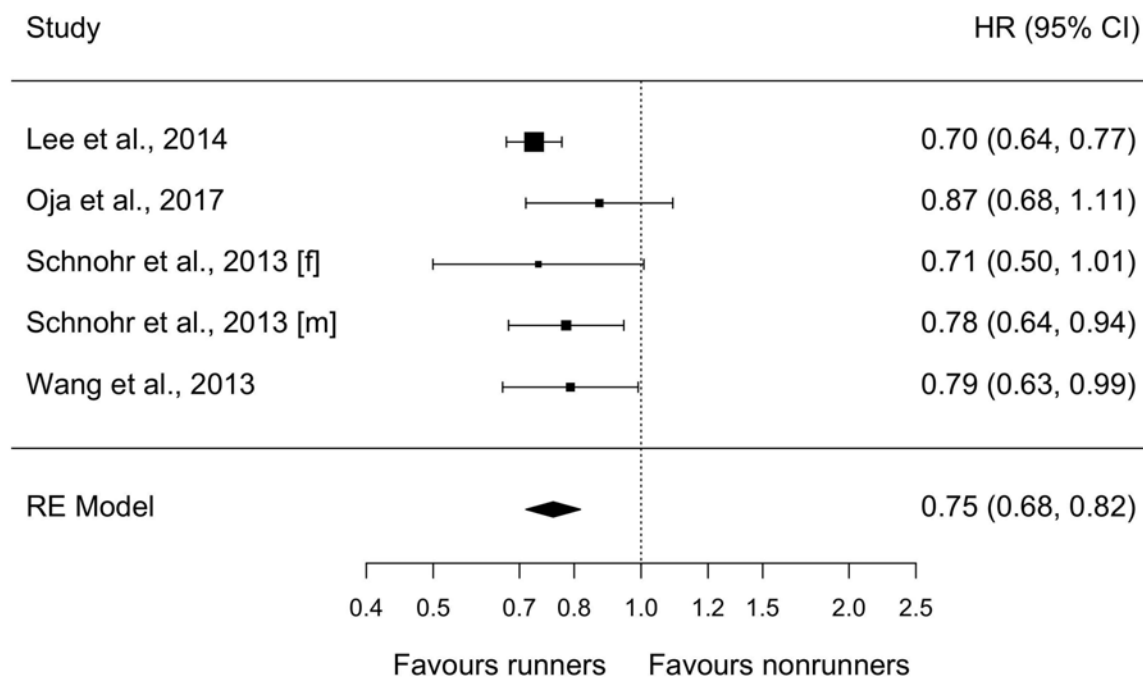
“-” =criteria not met; “*”=one point for meeting criteria; “**”=two points for meeting criteria; Overall score: 0-3 points = “poor quality”; 4-6 points = “fair quality”; 7-9 points = “good quality”
Lee et al (2016a) = reference number 30; Lee et al (2016b) = reference number 50

Supplementary table 4 Association between the dose or running and the risk of all-cause mortality: meta-regression estimates for the linear trend

Type of dose	β_0 (95% CI)	β_1 (95% CI)	p
Weekly frequency (days)	0.56 (0.36, 0.76)	0.03 (-0.02, 0.08)	0.202
Weekly duration (minutes)	0.66 (0.52, 0.80)	0.00 (0.00, 0.00)	0.923
Pace (mph)	1.03 (0.13, 1.93)	-0.05 (-0.19, 0.08)	0.448
Total volume (MET-minutes/week)	0.64 (0.44, 0.84)	0.00 (0.00, 0.00)*	0.634

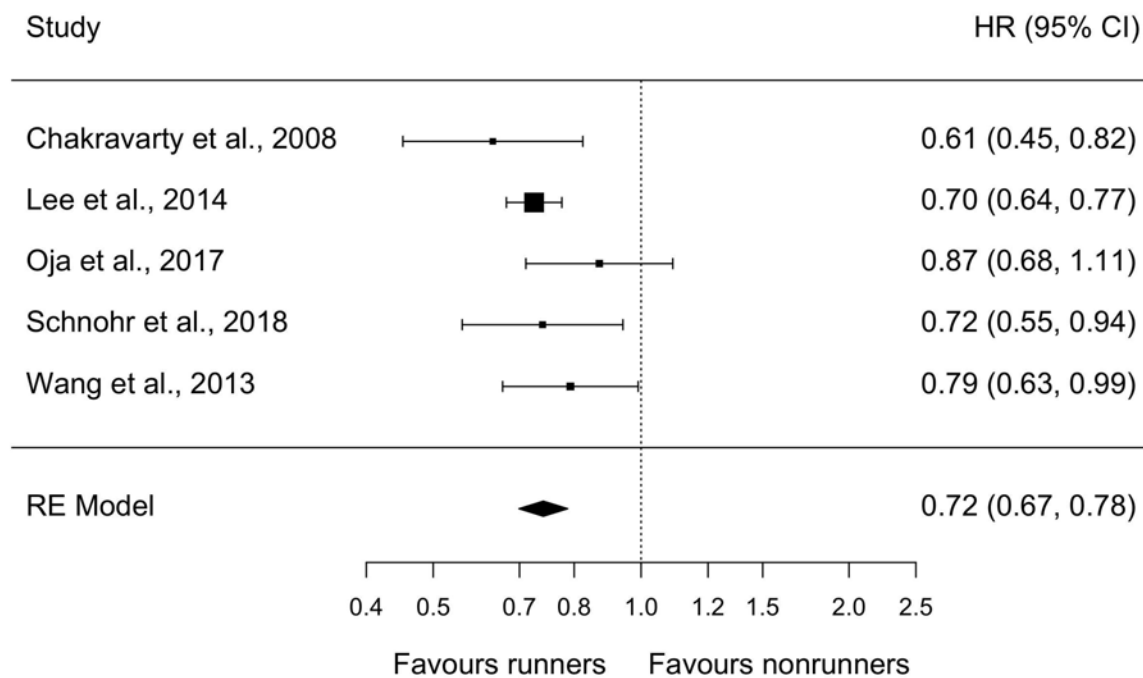
β_0 =intercept; 95% CI=95 percent confidence interval; β_1 =unstandardised regression coefficient; p =p-value for the linear trend; *Given that MET-minutes/week is a very small unit size to express the total volume of running, the following, precise β_1 (95% CI) should be used to calculate the estimated pooled HR: 5.57e-05 (95% CI: -6.50e-05, 1.77e-04)

Supplementary figure 1 Running participation and all-cause mortality risk: a sensitivity meta-analysis of hazard ratios including only the studies classified as being of “good quality”



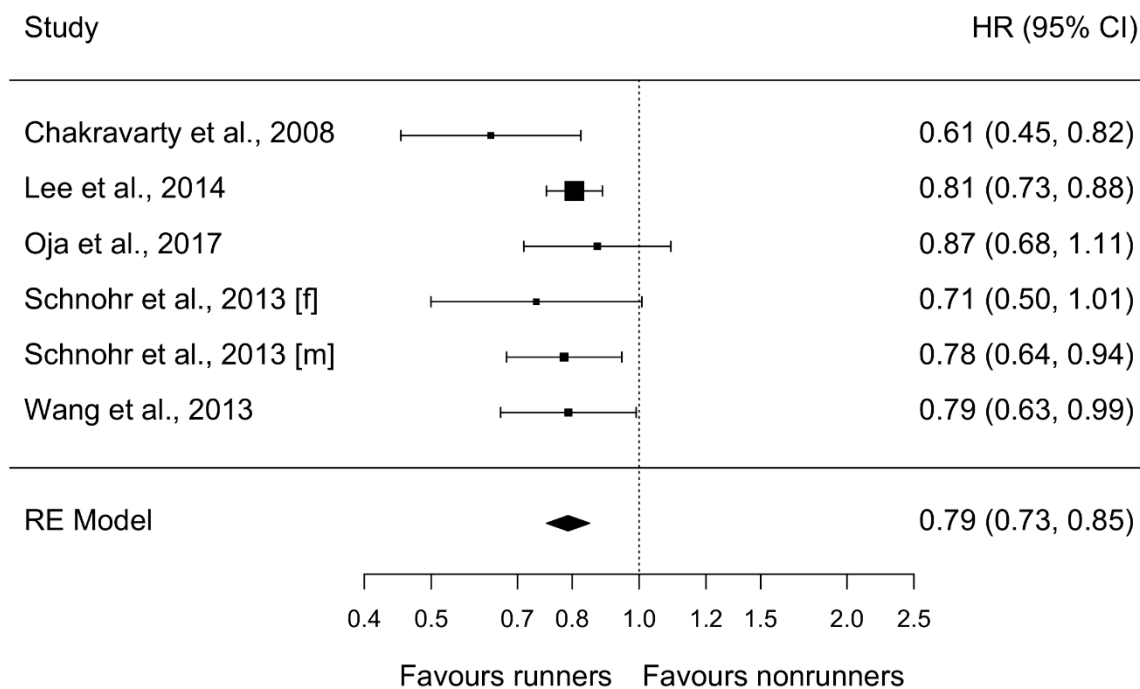
Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, with the overall score of 7-9 points being classified as “good quality”; HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity $I^2 = 18.07\%$ ($p = 0.453$)

Supplementary figure 2 Running participation and all-cause mortality risk: a sensitivity meta-analysis including the most recent study from the Copenhagen City Heart Study cohort



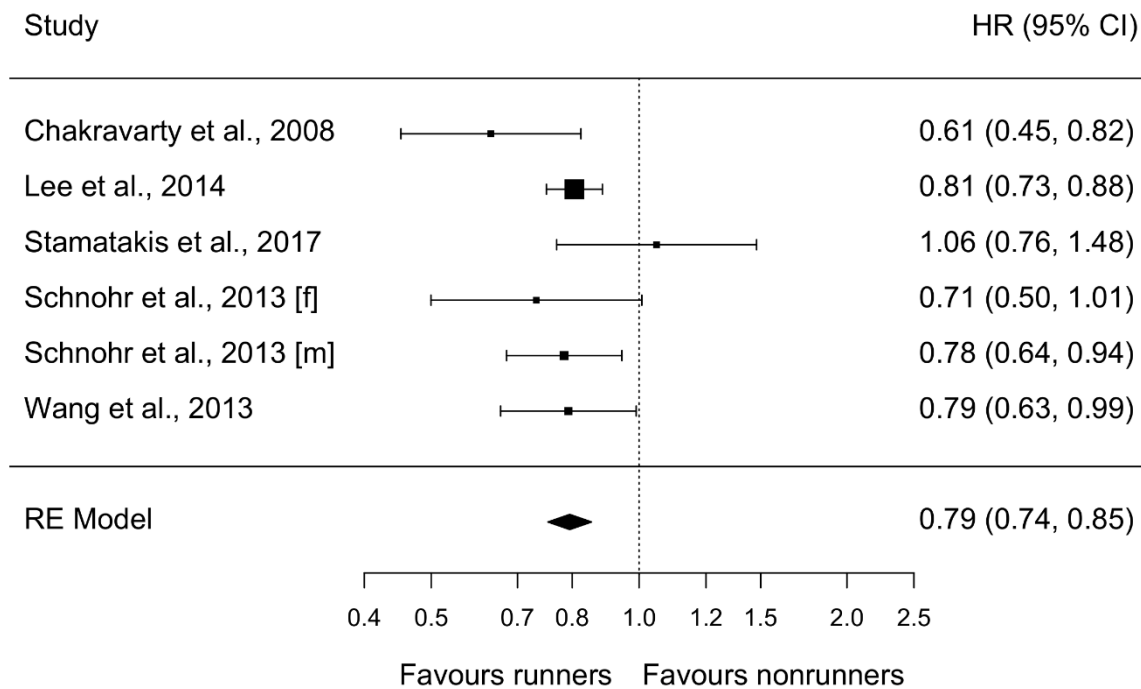
Schnohr et al. (2018) included only participants who participated in the third examination (1991-1994), which resulted in a shorter follow-up, a lower sample size, and a lower number of deaths when compared to a previous study from the same cohort; HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity $I^2 = 5.13\%$ ($p = 0.346$)

Supplementary figure 3 Running participation and all-cause mortality risk: a sensitivity meta-analysis including HRs from an alternative model in Lee et al. (2014) study



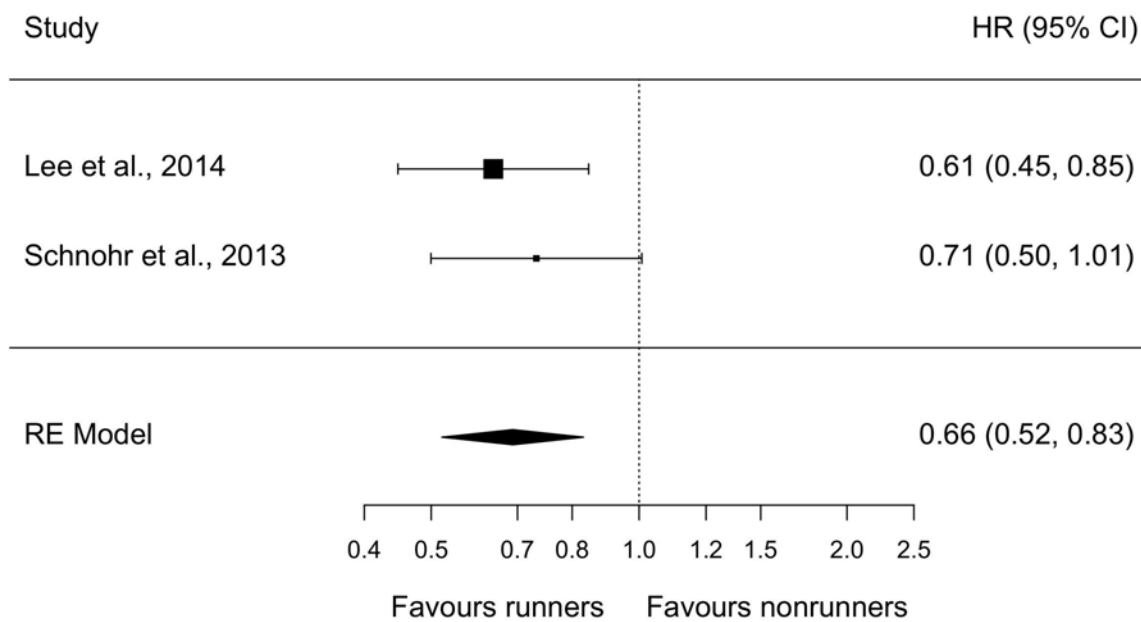
A description of the model from the Lee et al. (2014) study can be found in online supplementary table 1 (Model 2); HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity I^2 < 0.001% ($p = 0.550$)

Supplementary figure 4 Running participation and all-cause mortality risk: a sensitivity meta-analysis including HRs from an alternative model in Lee et al. (2014) study and from Stamatakis et al. (2017) study



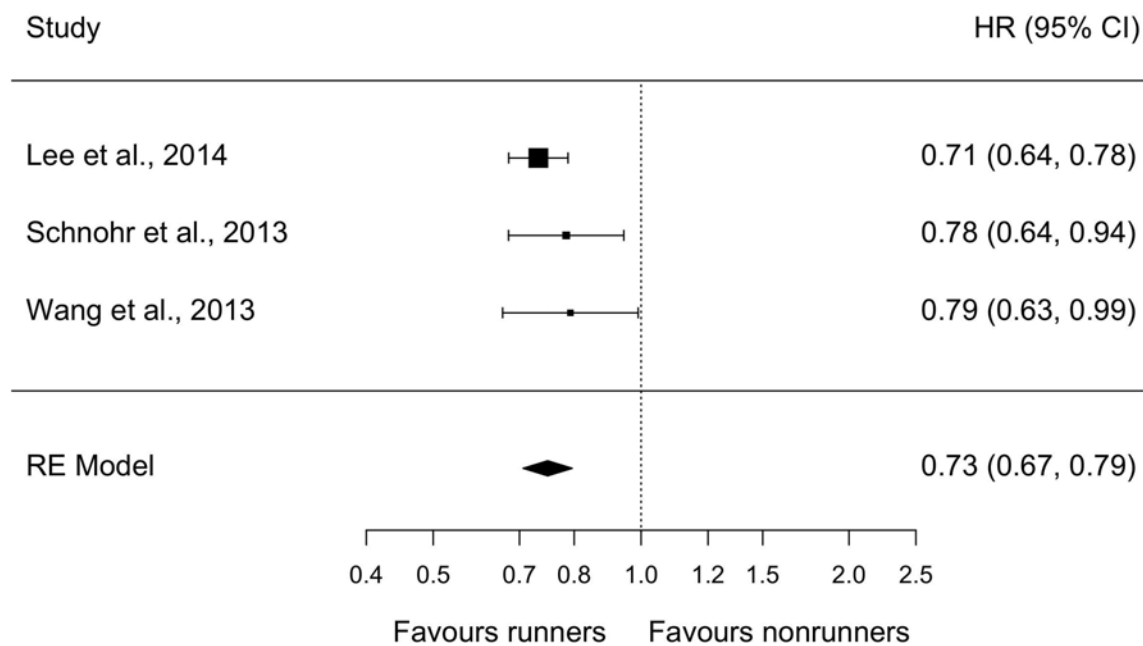
A description of the model from the Lee et al. (2014) study can be found in online supplementary table 1 (Model 2); HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity $I^2 = 0.01\%$ ($p = 0.271$)

Supplementary figure 5 Running participation and all-cause mortality risk among females:
a meta-analysis of hazard ratios



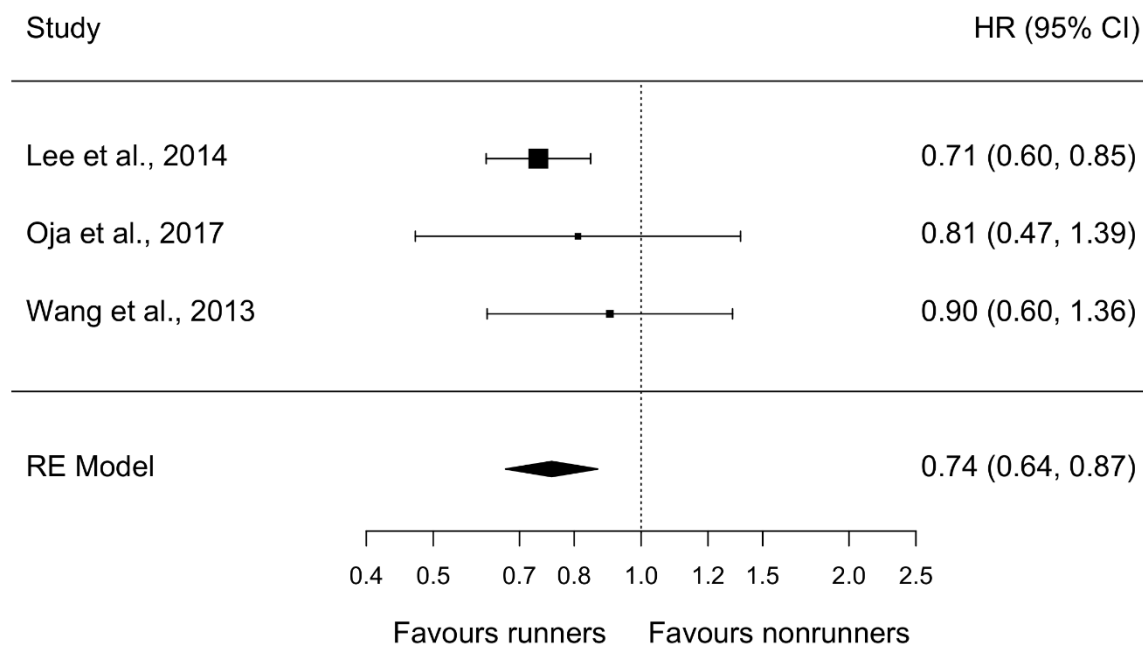
HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity I^2 < 0.001% ($p = 0.553$)

Supplementary figure 6 Running participation and all-cause mortality risk among males: a meta-analysis of hazard ratios



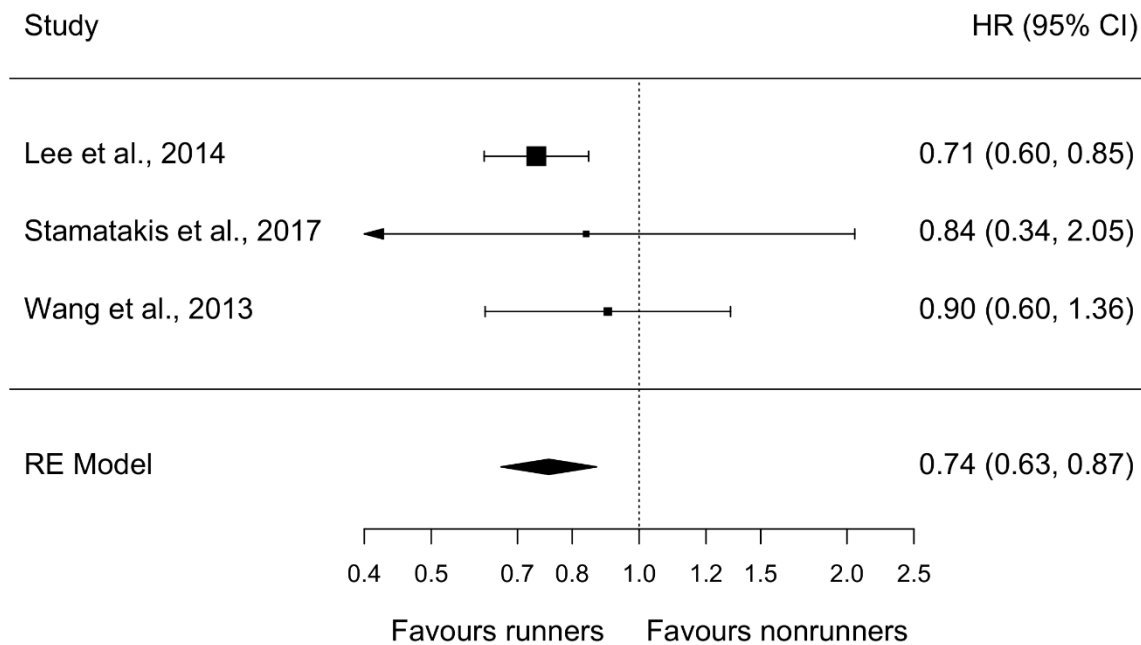
HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity I^2 < 0.001% ($p = 0.547$)

Supplementary figure 7 Running participation and cardiovascular mortality risk: a sensitivity meta-analysis including HRs from an alternative model in Lee et al. (2014) study



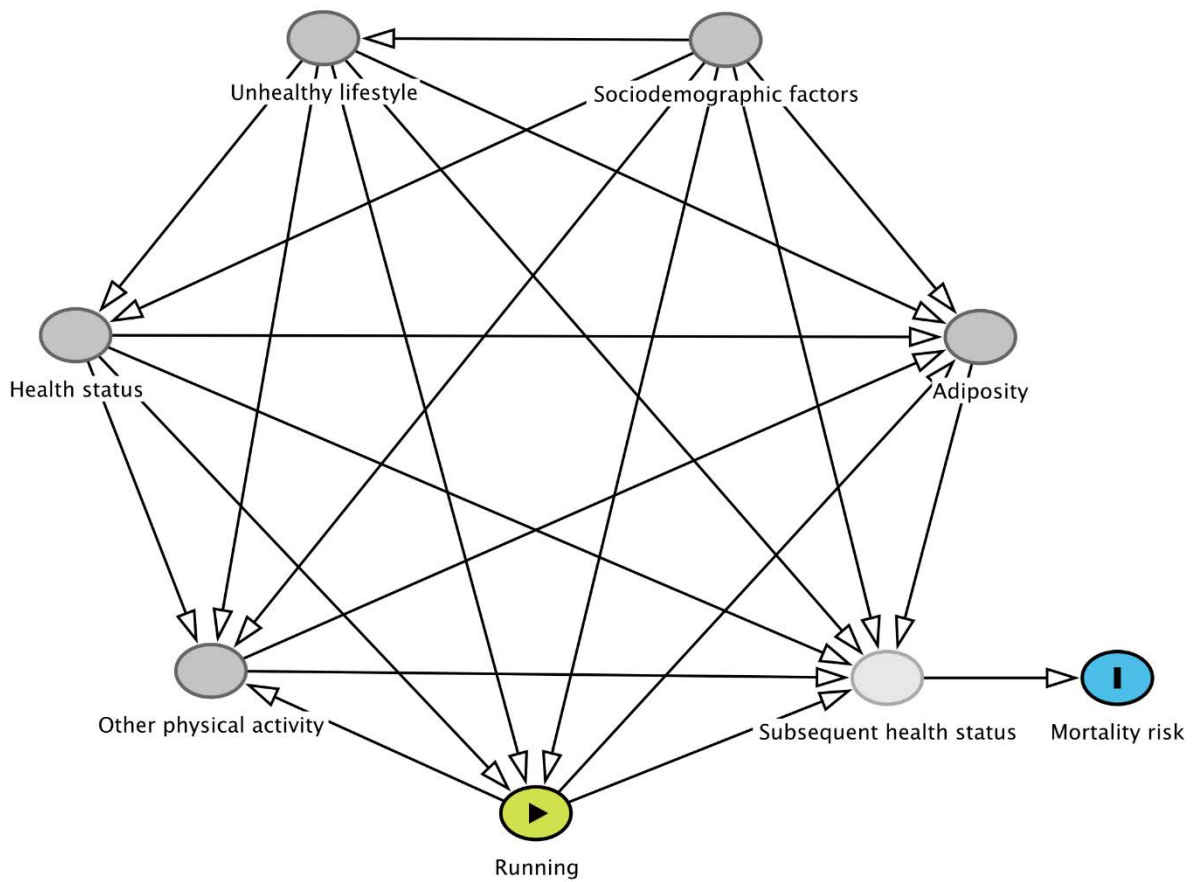
A description of the model from the Lee et al. (2014) study can be found in online supplementary table 1 (Model 2); HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity I^2 < 0.001% (p = 0.546)

Supplementary figure 8 Running participation and cardiovascular mortality risk: a sensitivity meta-analysis including HRs from an alternative model in Lee et al. (2014) study and from Stamatakis et al. (2017) study



A description of the model from the Lee et al. (2014) study can be found in online supplementary table 1 (Model 2); HR=adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI=95% confidence interval for HR; RE Model=pooled effect size from a random-effects meta-analysis model; p -value for the pooled HR <0.001; Heterogeneity $I^2 = 0.43\%$ ($p = 0.554$)

Supplementary figure 9 A possible alternative directed acyclic graph for the relationship between running participation and mortality risk



Green circle = exposure; blue circle = outcome; light grey circle = unobserved variable; dark grey circle = other variable; arrow = the direction of the causal relationship